7. Schulman KA, Glick HA, Rubin H, Eisenberg JM. Cost-effectiveness of HA-1A monoclonal antibody for gram-negative sepsis: economic assessment of a new therapeutic agent. JAMA 1991;266:3466-71.
8. Wenzel R, Bone R, Fein A, et al. Results of a second double-blind, randomized, controlled trial of antiendotoxin antibody E5 in gram-negative sepsis. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991. Washington, D.C.: American Society for Microbiology, 1991:294. (extended abstract.)
9. Warren HS, Danner RL, Munford RS. Anti-endotoxin monoclonal antibodies. N Engl J Med 1992;326:1153-7.
10. Ziegler EJ, Smith CR. Anti-endotoxin monoclonal antibodies. N Engl J Med 1992;326:1165.
11. Kunin CM. Problems in antibiotic usage. In: Mandell GL, Douglas RG Jr, Bennett JE, eds. Principles and practice of infectious diseases. 3rd ed. New York: Churchill Livingstone, 1990:427-34.
12. Wenzel RP, Andriole VT, Bartlett JG, et al. Anti-endotoxin monoclonal antibodies for gram-negative sepsis: guidelines from the Infectious Diseases Society of America. Clin Infect Dis 1992;14:973-6.
13. Bone RC, Fisher CJ Jr, Clemmer TP, et al. Sepsis syndrome: a valid clinical entity. Crit Care Med 1989;17:389-93.

SOUNDING BOARD

ANTI-ENDOTOXIN MONOCLONAL ANTIBODIES

SEVERAL monoclonal antibodies directed against bacterial lipopolysaccharide (endotoxin) are being developed for the adjunctive treatment of gram-negative sepsis. Two of these, E5 (XOMA, Berkeley, Calif.)[1] and HA-1A (Centocor, Malvern, Pa.),[2] have been studied in clinical trials and evaluated by the Food and Drug Administration for use in the United States. An open advisory-committee meeting was held by the FDA on September 4, 1991, at which new information was presented about the preclinical and clinical studies of these two products.[3] This article discusses some of the issues relating to the development and evaluation of these agents in the context of this new information. We focus on HA-1A because the analysis by the FDA of recently submitted data on E5 was not complete at the time of the meeting. On the basis of currently available preclinical and clinical data, we believe that a second placebo-controlled clinical trial of HA-1A is warranted to determine whether it should be widely used.

PRECLINICAL STUDIES

Unfortunately, there are few published data on E5 and HA-1A. The reports leave unanswered many questions concerning the epitopic specificity, binding characteristics, and biologic effects of these antibodies.

E5 is a murine IgM monoclonal antibody, raised in mice immunized with *Escherichia coli* J5, that binds to an epitope on lipid A.[1] It has been reported to bind to heterologous smooth lipopolysaccharide.[1,4,5] Two reports have addressed the ability of E5 to protect animals against endotoxin or bacterial challenge. In one study, E5 only minimally diminished the physiologic responses to lipopolysaccharide in sheep.[6] In another study, E5 added only slightly to the protection provided by antibiotics in mice challenged with gram-negative bacteria.[7]

HA-1A is a human IgM monoclonal antibody that binds to lipid A.[2,8,9] It was derived from a heterohybridoma created from the spleen cells of a patient who had been vaccinated with *E. coli* J5 before splenectomy.[10] The IgM produced by this hybridoma was initially described as binding specifically to a broad spectrum of smooth lipopolysaccharides and bacteria in an enzyme-linked immunosorbent assay.[10] Subsequent reports have suggested that HA-1A binds poorly to smooth lipopolysaccharide in such assays,[8,11] but that it binds to some types of smooth lipopolysaccharide in fluid phase, as measured by rate nephelometry.[9] This technique, however, may detect low-affinity as well as high-affinity interactions between antibody and antigen. A recent report[8] and information presented at the FDA meeting[9] suggest that HA-1A binds only slightly to smooth bacteria that have not been exposed to antibiotics. A different group found that IgM purified from the same hybridoma did bind to gram-negative bacteria, but that it also bound to gram-positive bacteria, fungi, cardiolipin, and lipoproteins, raising doubt about its specificity.[11] There is very little information on the ability of HA-1A to neutralize lipopolysaccharide in functional in vitro assays. Discussion at the FDA meeting suggested that it may decrease the lipopolysaccharide-induced production of tumor necrosis factor in cells obtained from leukapheresis packs, but not in whole blood,[12] a more physiologic assay.

Five studies have been published on the ability of the IgM produced by this hybridoma to protect against lipopolysaccharide challenge in animal models. The initial study reported that the hybridoma culture medium protected mice from lethal bacteremia and rabbits from the dermal Shwartzman reaction.[10] A subsequent abstract indicated that the IgM decreased mortality among neutropenic rabbits with pseudomonas bacteremia.[13] However, the same IgM provided only moderate protection from lipopolysaccharide-induced lung injury in rats[14] and did not prevent lipopolysaccharide-induced hypotension in rabbits.[15] Other investigators were unable to reproduce the protective effect against the dermal Shwartzman reaction or to detect protection in sensitized mice treated with an IgM prepared from the same hybridoma.[16] The ability of HA-1A to protect animals from endotoxin challenge was also discussed in the FDA meeting. It was noted by a company representative[17] that

> the results are not consistently reproducible over time and from laboratory to laboratory. This lack of reproducibility has troubled workers in the field of anti-endotoxin antibodies for many years and it leads us to the conclusion that these models would not be reliable as routine potency and release assays.

Thus, two problems involving the preclinical studies of HA-1A have become apparent. First, the data on binding that were presented in the initial description of the antibody[10] and endorsed in the publi

study[2] are substantially different from those more recently described by the company,[8] by participants at the FDA open meeting,[9] and by other investigators.[11] Second, there is no experimental model in which HA-1A has consistently protected animals from endotoxic challenge.[17] These difficulties seriously erode the stated rationale for the clinical study[2] and underscore the fact that the premise on which this approach is based remains unproved and unclear.[11,18] They also bring out the practical problem that there is no established method to ensure quality control of the antibody, since the characteristics of HA-1A that are related to protection are unknown.

Clinical Studies

E5 has been tested in two placebo-controlled clinical trials. In the first trial,[1] 486 patients with signs of gram-negative infection and a systemic septic response were enrolled. The administration of E5 was associated with increased survival only in the relatively small number of patients with gram-negative sepsis who were not in refractory shock (137 patients). In this subgroup of patients, 43 percent of those given placebo and 30 percent of those given E5 died within 30 days after treatment ($P = 0.01$). A second large trial (847 patients) was then conducted to test the hypothesis that E5 benefits patients with gram-negative sepsis who are not in refractory shock.[19] E5 did not improve survival in the 530 patients with documented gram-negative sepsis. A trend toward improved survival was observed in a subgroup of patients with major-organ failure without refractory shock (139 patients), but a detailed independent analysis of these data has not been presented.

HA-1A has been studied in a single, randomized, placebo-controlled clinical trial of patients with presumed gram-negative sepsis and was reported to prevent mortality in a subgroup of patients who had gram-negative bacteremia, whether or not they were in shock.[2] Although this investigation was carefully designed, questions have arisen concerning the demonstration of therapeutic efficacy, and the data analysis presented at the FDA meeting[20] differed from that reported by Ziegler et al.[2]

Our concern, which we discuss here, is that a significant result was found in only one of many overlapping subgroups; that the statistical result was marginal; that a protective effect was seen only at clinical centers with high mortality and only in patients with shock; that the APACHE II system used to stratify patients may have been inappropriately applied; that patients who received inadequate or unknown antibiotic treatment were included in the analysis; and that the data were not stratified according to the time elapsed before the antibody or placebo was infused.

Patient subgroups in the HA-1A trial were clearly defined in advance of analysis.[20] Anticipated covariates were specified and provisions were described for making certain key judgments (such as whether or not a patient had received adequate antimicrobial therapy, or whether a death was unrelated to sepsis) before the study code was broken. The three primary subgroups used in the analysis of efficacy were (in order of importance) patients with gram-negative sepsis, who had documented infection with gram-negative organisms (with or without bacteremia) but not infection with other microbes; patients with gram-negative bacteremia, who had positive blood cultures for gram-negative bacteria, whether or not they had positive cultures for other microbes; and patients with gram-negative infection, who consisted of all patients with gram-negative disease, regardless of other kinds of ongoing infection. In addition, two categories of mortality (mortality due to sepsis and mortality due to all causes) were analyzed for two times after infusion (at 14 days and over a 28-day period). Mortality due to sepsis was identified as the more important indicator of efficacy.[20] The FDA analysts suggested that because multiple comparisons were made in the analysis (three subgroups, two categories of mortality, and two observation periods), the level of statistical significance should be adjusted: for a statistically significant difference, it was recommended that the necessary P value should be below a level that was somewhere between 0.01 and 0.03.[21]

According to these guidelines, HA-1A was found to be associated with a beneficial outcome in only one of the three subgroups in the efficacy analysis (patients who had gram-negative bacteremia) and in relation to only one of the end points (mortality from all causes over the 28-day period)[20] (Table 1). During the last two weeks of the trial, four deaths that were not due to sepsis occurred in the placebo group; excluding these deaths from the analysis raised the P value from 0.014 (the P value for mortality due to all causes) to 0.039 (the P value for mortality due to sepsis), which was not within the estimated range of values that would show a statistically significant result.[21] The drug was not effective in the subgroup with gram-negative sepsis. Furthermore, among the 201 patients with nonbacteremic gram-negative infections, mortality was somewhat higher in the HA-1A group than in the placebo group at both 14 and 28 days.[22]

Data were also presented at the FDA meeting regarding the effect of HA-1A in subgroups of patients with gram-negative bacteremia, according to the presence or absence of shock[23] (Table 2). The published report, in which analysis was based on a Cox proportional-hazards model, stated that "HA-1A reduced mortality in both patients with shock and patients without shock."[2] In contrast, the FDA, analyzing the same data according to different statistical methods, came to the following conclusion: "in the no-shock group there was not a significant difference in mortality. . . . If you look over time, those curves cross. At some time periods it is higher in the treatment group and, in others, in the placebo. There does not appear to be a significant difference."[23] Although the study was not primarily designed to examine this issue, these data suggest that the benefit of HA-1A among patients with gram-negative bacteremia may be limited

to patients with gram-negative bacteremia who are in shock.

Patients who receive inadequate antimicrobial chemotherapy present a special problem in trials of anti-endotoxin antibodies. Anti-endotoxin monoclonal antibodies are usually thought to be adjunctive therapy; they should probably not be expected to benefit patients who receive inadequate antimicrobial chemotherapy. This point would seem to apply particularly to HA-1A, since the available data suggest that HA-1A binds only slightly to bacteria that have smooth lipopolysaccharide (i.e., most blood isolates), unless the bacteria have been treated with antibiotics.[8,9] In the placebo group of the HA-1A trial, inappropriate antimicrobial therapy was strongly associated with death in patients with gram-negative bacteremia (mortality of 69 percent with inappropriate therapy and 27 percent with appropriate therapy).[24] Patients who received inadequate antimicrobial chemotherapy were not excluded from the analysis of the HA-1A trial; instead, patients with inadequate or unknown antimicrobial therapy were included in the multivariate analysis (16 patients in the placebo group [17 percent] and 10 in the HA-1A group [10 percent]).[20] When only patients who received adequate antimicrobial therapy were considered in the analysis of mortality after 14 days, there was no significant difference between the two groups of patients with gram-negative bacteremia (21 deaths among 79 patients in the placebo group and 20 deaths among 95 patients in the HA-1A group [data from slides presented at the FDA meeting (Siegel JP)][20]). Data were not presented at the FDA meeting concerning deaths at the 28-day end point.

The HA-1A clinical trial took place at 22 study sites. Analysis of the consistency of the drug effect at the sites where at least one patient with gram-negative bacteremia was included in each study group and at least one patient died indicated that many more study sites found lower mortality in the HA-1A group than found it in the placebo group (11 sites vs. 1 site).[25] This apparent consistency among study sites may be important evidence that the effect of HA-1A is genuine. However, concern was raised at the FDA meeting about another feature of the distribution of patients among the study sites. As a panelist[26] pointed out,

> Six of the 22 sites had more than 50-percent mortality in the placebo group and 16 of them had less than that. . . . All of the effect is in the high-mortality sites within the gram-negative bacteremia group, so that there is a 64-percent mortality in the placebo group and 22 percent in the HA-1A, whereas, actually, there is a slight advantage to placebo in the low-mortality sites.

The ensuing discussion did not explain why HA-1A might have its effect principally in patients at centers that had high case fatality rates for gram-negative bacteremia.

Table 1. Mortality Due to Sepsis and All Causes in the HA-1A Trial, According to Patient Subgroup.*

Subgroup	Mortality at 14 Days Due to Sepsis and All Causes†		P Value		
	Placebo	HA-1A	Sepsis		All causes
			day 14†	over 28 days	over 28 days
	patients dead/all patients (%)				
Gram-negative sepsis	47/145 (32)	40/137 (29)	0.56	0.29	0.18
Gram-negative bacteremia	32/95 (34)	25/105 (24)	0.12	0.039	0.014
Gram-negative infection	61/207 (29)	56/194 (29)	0.89	0.47	0.30

*Adapted from slides presented at the FDA meeting (Siegel JP).[20]
†Mortality due to sepsis equaled mortality due to all causes at 14 days.

The published clinical studies on E5 and HA-1A[1,2] both used the APACHE II scoring system[27] to stratify patients according to physiologic status and underlying disease severity at the time of entry. Neither investigation fully considered the nonlinear relation between APACHE II score and the risk of hospital death.[27,28] Instead of using the raw APACHE II score in multivariate analysis, it would have been more informative to calculate and enter the risk of death during hospitalization in each patient. For example, the APACHE II equation that relates a raw score to the risk of in-hospital death gives great weight to emergency surgery as an independent risk factor; depending on the raw APACHE II score, emergency surgery can add as much as 14 percent to the risk of in-hospital death. Using individual risks rather than the raw APACHE II scores in the multivariate analysis might have controlled more accurately for an imbalance in the distribution of major underlying disorders in the HA-1A trial — which, in this instance, favored the HA-1A group.[18] The placebo group contained more patients with disseminated intravascular coagulation (21 percent vs. 18 percent), adult respiratory distress syndrome (13 percent vs. 9 percent), acute hepatic failure (26 percent vs. 19 percent), acute renal failure (46 percent vs. 35 percent), and recent surgery (34 percent vs. 29 percent).[2]

The published report describing the HA-1A trial indicated that "The *median* [emphasis added] intervals between the diagnosis of sepsis and infusion of the study drug were 9.3 hours in the placebo group and 14.3 hours in the HA-1A group."[2] It was stated in the FDA meeting that the *mean* interval before infusion in

Table 2. Mortality due to Sepsis in Patients with Gram-Negative Bacteremia, According to the Presence or Absence of Shock.*

	Mortality at Day 14			Mortality over 28 Days
	Placebo	HA-1A	P value	P value
	patients dead/all patients (%)			
All patients	32/95 (34)	25/105 (24)	0.12	0.039
Patients with shock	23/48 (48)	13/54 (24)	0.012	0.023
Patients without shock	9/47 (19)	12/51 (24)	0.60	—

*Adapted from slides presented at the FDA meeting (Siegel JP).[20]

both groups was approximately 20 hours,[29] indicating that many of the patients received HA-1A or placebo a very long time after the onset of sepsis. Unfortunately, there are no available data that reveal the efficacy of the drug according to the interval between the onset of sepsis or shock and the infusion. This information is of obvious importance to clinicians. The possible role of differences in the time of administration of HA-1A or placebo in determining the outcome of the trial is also impossible to evaluate without further data. Nevertheless, the time of drug administration may be a very important determinant of clinical outcome. According to the FDA analyst, "on the treatment day and the day immediately thereafter, is where the largest evidence of effect and most of the difference between the treatment groups occurred."[30] During this period, 13 percent of the patients given placebo died, as compared with 5 percent of those given HA-1A.[30] Much more information is needed about this aspect of the HA-1A trial.

Conclusion

Although there are few data available on preclinical studies of E5, the available data from the two clinical trials suggest that E5 does not reproducibly prevent mortality in patients with gram-negative sepsis, even in those who are not in refractory shock. A more complete picture may emerge when the results of the second E5 study are fully analyzed.

In our opinion, the evidence that HA-1A reduces mortality among patients with gram-negative bacteremia is suggestive but not conclusive. A significant result was found in only one of many possible subgroup–end-point categories, and HA-1A was not shown to prevent death due to the condition that it was intended to treat — gram-negative sepsis. Post hoc analysis of prospective studies should always be interpreted cautiously. Nevertheless, the flaws in the scientific foundation used to justify a clinical trial of HA-1A, the uncertainties about the analysis of that trial, and the marginal statistical significance of the result ("borderline," according to a statistical consultant to the FDA[31]) persuade us that the null hypothesis has not been convincingly rejected in the HA-1A study. An accurate determination of efficacy seems especially important for HA-1A: even if the drug is used according to the criteria for study entry, it will potentially benefit a very small fraction of the patients who receive it, and its cost is substantial (currently over $3,500 per dose in Europe). The use of such an expensive therapy in an appropriate and cost-effective manner requires conclusive knowledge of its efficacy.

The inconsistent outcomes of the two E5 trials,[1,19] as well as previous experience in the evaluation of corticosteroid therapy for sepsis,[32-35] support the view that it is difficult to test a therapeutic agent in this complex population and obtain the same result twice. It should be noted that the HA-1A trial is not a confirmation of the earlier trial of polyclonal antiserum to *E. coli* J5[36]; HA-1A is a new agent, and the protective factor in the polyclonal antiserum remains unknown and controversial. Accordingly, we believe that the use of HA-1A should remain experimental until a second randomized, placebo-controlled trial has confirmed its efficacy. This trial would test the treatment hypothesis generated by the first trial — that HA-1A increases survival when given early to patients with presumed gram-negative bacteremia who are in septic shock.

Massachusetts General Hospital
Boston, MA 02114 — H. Shaw Warren, M.D.

National Institutes of Health
Bethesda, MD 20205 — Robert L. Danner, M.D.

University of Texas
Southwestern Medical Center
Dallas, TX 75235 — Robert S. Munford, M.D.

Dr. Munford shares a patent for the purification of acyloxyacyl hydrolase.

References

1. Greenman RL, Schein RMH, Martin MA, et al. A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of gram-negative sepsis. JAMA 1991;266:1097-102.
2. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin — a randomized, double-blind, placebo-controlled trial. N Engl J Med 1991;324:429-36.
3. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991. (Obtained through the Freedom of Information Act.)
4. Gazzano-Santoro H, Parent JB, Wood DM, et al. Reactivity of E5 monoclonal antibody to smooth lipopolysaccharides. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991. Washington, D.C.: American Society for Microbiology, 1991:230. abstract.
5. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:179-85. (Obtained through the Freedom of Information Act.)
6. Wheeler AP, Hardie WD, Bernard G. Studies of an antiendotoxin antibody in preventing the physiologic changes of endotoxemia in awake sheep. Am Rev Respir Dis 1990;142:775-81.
7. Young LS, Gascon R, Alam S, Bermudez LEM. Monoclonal antibodies for treatment of gram-negative infections. Rev Infect Dis 1989;11:Suppl 7:S1564-S1571.
8. Bogard WC Jr, Siegel SA. The human monoclonal antibody HA-1A: studies on the epitope location within the endotoxin molecule and epitopic exposure on the surface of viable gram-negative bacteria. Circ Shock 1991;34:119. abstract.
9. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:41-3. (Obtained through the Freedom of Information Act.)
10. Teng NNH, Kaplan HS, Hebert JM, et al. Protection against gram-negative bacteremia and endotoxemia with human monoclonal IgM antibodies. Proc Natl Acad Sci U S A 1985;82:1790-4.
11. Baumgartner J-D, Heumann D, Glauser M-P. The HA-1A monoclonal antibody for gram-negative sepsis. N Engl J Med 1991;325:281-2.
12. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:82-4. (Obtained through the Freedom of Information Act.)
13. Ziegler EJ, Teng NNH, Douglas H, Wunderlich A, Berger HJ, Bolmer SD. Treatment of Pseudomonas bacteremia in neutropenic rabbits with human monoclonal IgM antibody against *E. coli* lipid A. Clin Res 1987;35:619A. abstract.
14. Feeley TW, Minty BD, Scudder CM, Jones JG, Royston D, Teng NNH. The effect of human antiendotoxin monoclonal antibodies on endotoxin-induced lung injury in the rat. Am Rev Respir Dis 1987;135:665-70.

15. Tune BM, Hsu CY, Bieber MM, Teng NNH. Effects of anti-lipid A human monoclonal antibody on lipopolysaccharide-induced toxicity to the kidney. J Urol 1989;141:1463-6.
16. Baumgartner JD, Heumann D, Gerain J, Weinbreck P, Grau GE, Glauser MP. Association between protective efficacy of anti-lipopolysaccharide (LPS) antibodies and suppression of LPS-induced tumor necrosis factor alpha and interleukin 6: comparison of O side chain-specific antibodies with core LPS antibodies. J Exp Med 1990;171:889-96.
17. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:50. (Obtained through the Freedom of Information Act.)
18. Zanetti G, Glauser MP, Baumgartner JD. Use of immunoglobulins in prevention and treatment of infection in critically ill patients: review and critique. Rev Infect Dis 1991;13:985-92.
19. Wenzel R, Bone R, Fein A, et al. Results of a second double-blind, randomized, controlled trial of antiendotoxin antibody E5 in gram-negative sepsis. In: Program and abstracts of the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, September 29–October 2, 1991. Washington, D.C.: American Society for Microbiology, 1991:294. (and extended abstract.)
20. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:99-124. (Obtained through the Freedom of Information Act.)
21. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:104-7. (Obtained through the Freedom of Information Act.)
22. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:118. (Obtained through the Freedom of Information Act.)
23. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:109. (Obtained through the Freedom of Information Act.)
24. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:111-2. (Obtained through the Freedom of Information Act.)
25. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:116-7. (Obtained through the Freedom of Information Act.)
26. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:148. (Obtained through the Freedom of Information Act.)
27. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification. Crit Care Med 1985;13:818-29.
28. Knaus WA, Wagner DP, Lynn J. Short-term mortality predictions for critically ill hospitalized adults: science and ethics. Science 1991;254:389-94.
29. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:144. (Obtained through the Freedom of Information Act.)
30. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:114-5. (Obtained through the Freedom of Information Act.)
31. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:154. (Obtained through the Freedom of Information Act.)
32. Schumr W. Steroids in the treatment of clinical septic shock. Ann Surg 1976;184:333-41.
33. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock — a prospective, controlled study. N Engl J Med 1984;311:1137-43.
34. Bone RC, Fisher CJ Jr, Clemmer TP, et al. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. N Engl J Med 1987;317:653-8.
35. The Veterans Administration Systemic Sepsis Cooperative Study Group. Effect of high-dose glucocorticoid therapy on mortality in patients with clinical signs of systemic sepsis. N Engl J Med 1987;317:659-65.
36. Ziegler EJ, McCutchan JA, Fierer J, et al. Treatment of gram-negative bacteremia and shock with human antiserum to a mutant *Escherichia coli*. N Engl J Med 1982;307:1225-30.

CORRESPONDENCE

EFFECTS OF RESTRICTIVE HANDGUN LAWS

To the Editor: Efforts to "prove" that the Washington, D.C., handgun ban (with a grandfather clause) — sometimes misleadingly referred to as a registration or licensing system — has been effective in reducing homicide have always had to disguise the fact that the city's homicide rate fell sharply between 1974 and 1976, to 26.9 per 100,000, before the law took effect in February 1977. Since then (1977 through 1991), the homicide rate has been higher than in 1976 every year except 1985 (23.5 per 100,000). In almost every year since 1976, the trend in homicide in the District of Columbia has compared unfavorably with the trend in the United States as a whole or in big cities generally[1] (and U.S. Bureau of the Census).

One previous effort averaged the homicide rates for the years 1974 through 1976 to produce a high pre-law rate to compare with a lower post-law average.[2] Another simply compared data for 1974 with data for 1978.[3] The latest effort, by Loftin et al. (Dec. 5 issue),[4] merely lengthens the pre-law period used for averaging, to include the years 1968 through 1976. The result misleadingly suggests a post-law decline in homicide (a sharp decline in gun-related homicide and a shallow one in homicide by other means). The drop did not occur. There were 15.7 criminal homicides per month in 1976 and 15.9 per month from 1977 to 1987.[1]

Loftin et al. enhanced their effort by using raw numbers instead of rates — an important factor given that the population of the District of Columbia fell about 20 percent in the course of the 20 years studied. Worse yet, the authors used the surrounding suburbs — and raw data — as controls, when the suburban population was increasing faster than the population of Washington was declining, and over twice as fast as their number of homicides were rising.[4] Baltimore, more similar to Washington than its suburbs, recorded a slightly greater drop in homicides per month (1977 through 1987 vs. 1968 through 1976)[1] than was claimed for Washington,[4] although its population was falling slightly less rapidly (U.S. Bureau of the Census). In addition, by stopping in 1987, the authors avoid the problem of the District of Columbia's recent record-setting years for homicide — with the number up 110 percent in Washington and 35 percent in Baltimore[1] — with the unscientific, "article of faith" assertion that the situation would have been worse but for the gun law.

Logically, the data conflict with what would have been expected, undermining the authors' contention that the "strongest argument for attributing the reduction . . . to the restrictive licensing law is the relative implausibility of alternative explanations." It is the gun-law explanation that is implausible. Even with the authors' faulty data, a prospective ban on handguns should have led to a gradual decline in the availability of guns, which, if related to homicide, should have meant — as the authors admit — a similar gradual decline in homicide instead of the sudden one that they claim.

If any of the difference in homicide trends is the result of my using data from the Federal Bureau of Investigation (FBI), as opposed to the authors' use of data from the National Center for Health Statistics (NCHS), and if there really has been a decline since 1976 according to the NCHS data, then the effect of the gun law has been to protect the lives of felons: A decline in "homicide and legal intervention" according to the NCHS, but not "murder and nonnegligent homicide" according to the FBI, means a decline in justifiable homicides by police and civilians, which are excluded from the FBI data and included in the NCHS data.

From the phrase "restrictive licensing" in its title — guns

banned may be acquired — onward, the article is dishonest, and the District of Columbia gun law can look effective only to gun control's true believers.

PAUL H. BLACKMAN, PH.D.
Washington, DC 20036 National Rifle Association of America

1. FBI uniform crime reports: crime in the United States, 1968–1990. Washington, D.C.: Government Printing Office, 1969–1991.
2. Nicholson R, Garner A. The analysis of the Firearm Control Act of 1975: handgun control in the District of Columbia. Washington, D.C.: U.S. Conference of Mayors, 1980.
3. Jones ED III. The District of Columbia's "Firearms Control Regulation Act of 1975": the toughest handgun control law in the United States — or is it? Ann Am Acad Polit Soc Sci 1981;455:138–49.
4. Loftin C, McDowall D, Wiersema B, Cottey TJ. Effects of restrictive licensing of handguns on homicide and suicide in the District of Columbia. N Engl J Med 1991;325:1615-20.

To the Editor: Loftin et al. demonstrate an association between a restrictive handgun law in Washington, D.C., and the number of homicides and suicides from 1976 through 1987. It would have been helpful if the authors had provided a breakdown of the nature of the homicides. They classified deaths according to the codes of the *International Classification of Diseases*. We are told that "unintentional deaths" and deaths in which "the intent was unknown" were excluded. How many of the homicides were crimes of passion involving normally law-abiding citizens whose tempers may have flared? How many involved law-abiding citizens justifiably defending themselves against a dangerous assault or defending their home during a break-in? Were these even classified as homicides? How many homicides were the result of a cocaine deal gone bad, in which one dealer may have shot another (or other similar violent crime)?

It is of course desirable to prevent any death, but should law-abiding citizens of this country be forced to forfeit personal freedoms to keep criminals from killing each other? Near the end of the article, Loftin et al. admit that "there have been dramatic increases in homicides very recently. . . ." Hmm — the law has not become less restrictive. This suggests that criminals have been able to circumvent the law, that the effect was only temporary. Of course, law-abiding citizens are still disarmed, making them potentially more vulnerable to violent crime. Perhaps, if more law-abiding citizens legally carried handguns, many criminals would be deterred from violent crime. The prospect of being shot by an intended victim may be a greater deterrent than is our present system of criminal justice. In Washington, D.C., deterrents grow less each year, and the city is paying a price for it in violent crime.

TIMOTHY WELLS, M.D.
Portland, ME 04102 Maine Medical Center

To the Editor: The study by Loftin et al. suggests that restrictive licensing of handguns in Washington, D.C., reduced the numbers of suicides and homicides in the city in the four-year period after it was enacted. The authors suggest that such restrictions have their greatest effect by reducing the number of situations in which the user selected a gun primarily because it was the most readily available weapon. Although there is considerable evidence supporting the "weapon-choice" theory, I would like to discuss some problems with it that are relevant to the findings on suicide rates in the study. The authors' study agreed with other studies demonstrating a correlation between lower rates of suicide by firearms and gun-control laws. However, although they found a reduction in the overall rate of suicide, the absence of a rise in suicides not committed with firearms does not prove that a substitution of other lethal means for guns did not occur.

Studies of handgun restrictions in two other cities did not demonstrate reductions in their overall suicide rates. According to a study of the suicide rate in the city of Toronto during five-year periods before and after the enactment of an even more restrictive gun law, a decrease in deaths by firearms was compensated for by an increase in deaths by leaping.[1] It would have been helpful to know the effects on the rate of suicide by jumping in the study by Loftin et al. The impact of changes in the availability or the lethality of a method of suicide will depend largely on the frequency of its use; death by jumping is common in cities because of the presence of subways, bridges, tall buildings, and moving automobiles, so it may be expected that jumping would be substituted as a method if an urban gun ban was enacted. However, a confounding variable in urban studies could be the possibility that some victims may not have been residents of the city but came into it only to commit suicide by jumping.

A study in the city of Vancouver, British Columbia, also failed to find any effect of gun laws on the overall rate of suicide there, although the laws had a significant effect in reducing the suicide rate among persons 15 to 24 years old.[2] The strong influence of age and sex on suicide is well known, and this suggests that it is necessary to employ statistics that are method-specific for age and sex in studies of gun laws. Although the study by Loftin et al. did control for changes in the age of the urban population, unless it is known that there was stability in such statistics in regard to methods of suicide, the overall impact of the gun ban on suicides not committed with firearms cannot be fully assessed.[3]

It is also necessary to increase the period of study to determine whether the effects of handgun restrictions will be sustained. The authors provide data on homicides during the years up to 1987; sadly, Washington, D.C., has surpassed its annual record for homicides for the fourth straight year since the study period ended.[4] The authors suggest that this was due to a variety of economic and social factors, particularly the spread of drugs such as crack cocaine. Although these are important factors, it should also be mentioned that even a tough gun law like the one in Washington, D.C., cannot stem the flow of guns into the city from the underground market and from sales in neighboring states. For this reason, only a strong federal law restricting or banning handguns can make a noteworthy and lasting impact on the epidemic of violence in our urban areas.

ROBERT EILERS, M.D.
Hammonton, NJ 08037 Ancora Psychiatric Hospital

1. Rich CL, Young JG, Fowler RC, Wagner J, Black NA. Guns and suicide: possible effects of some specific legislation. Am J Psychiatry 1990;147:342-6.
2. Sloan JH, Rivara FP, Reay DT, Ferris JAJ, Kellermann AL. Firearm regulations and rates of suicide: a comparison of two metropolitan areas. N Engl J Med 1990;322:369-73.
3. Eilers RP. Effects of gun laws on suicide rates. Am J Psychiatry 1991;148: 149-50.
4. Horwitz S, Duggan P. 3000 killings later — a generation addicted to violence. Washington Post. December 29, 1991:A1, A20-A21.

To the Editor: I am concerned about several aspects of the article by Loftin et al. (1) The study used data on homicides and suicides by all firearms to draw conclusions about a law that restricted handguns only. (2) The data on homicide do not differentiate between unjustifiable homicide (murder) and justifiable or excusable homicide (legitimate defense of innocent lives). (3) The "abruptness" of the alleged change is surely an artifact of the analytical method. Taking the mean on both sides of a fixed point will always generate a stepwise graph and may also disguise underlying variation. The shape of the graphs at least suggests that homicides and suicides peaked in the mid-1970s and began declining before the implementation of the gun law. (4) The study is one-sided in that it looks only at the negative aspects of firearms. A proper study would have tried to estimate the number of lives saved by private firearms in Washington, D.C., and come up with a net gain or loss of life. Would you evaluate a medical or surgical procedure strictly on the basis of morbidity and mortality rates, without considering its beneficial effects?

Particularly suspicious, in my opinion, is the authors' differing interpretation of other possible influences on homicide and suicide

ANTI-ENDOTOXIN MONOCLONAL ANTIBODIES

To the Editor: In this issue of the *Journal* Warren et al.[1] assess the evidence supporting the efficacy of HA-1A. Their synthesis of these data is largely subjective and differs substantially from the conclusions of the Food and Drug Administration advisory panel that voted unanimously to recommend the licensure of HA-1A.

During the past six years, the in vitro assays of HA-1A binding to endotoxins and lipid A have been refined. The current assays are reproducible and show binding to natural and synthetic lipid A, to rough and some smooth endotoxins, and to antibiotic-treated smooth bacteria.[2]

Human monoclonal antibodies against endotoxin may fail to demonstrate consistent protection in animal models of gram-negative bacteremia and endotoxemia, either because most animals are highly resistant to endotoxin and toxic-sensitization techniques or because large inoculums of bacteria or endotoxin are required to induce a lethal response. Also, the species of animals used in the laboratory are distinct from humans with respect to key immune defenses against endotoxin, such as complement-mediated immune adherence.[2] Thus, microbiologic, immunologic, and physiologic factors complicate the applicability of experimental results in animal models to the treatment of sepsis in humans. This is not a problem unique to the study of the immunotherapy of sepsis, and it certainly does not "erode the stated rationale for the clinical study."

Warren et al. do not mention that patients with gram-negative bacteremia were defined in the protocol as the group of primary interest, as the FDA pointed out.[2] Thus, the group with gram-negative bacteremia was not just one of many overlapping subgroups, and it certainly was not defined as a result of post hoc data analysis. Warren et al. emphasize mortality from sepsis as an important end point, but they do not report that Dr. O'Neill, the director of the FDA's Division of Biometrics, recommended that mortality from all causes be used as the primary end point.[2] Warren et al. have suggested that the statistical results were marginal. We disagree. The P value for mortality from all causes in the 200 patients with gram-negative bacteremia was 0.014; for those with shock, it was 0.017, and for those with shock and organ failure, 0.001. These results were robust and did not change substantially after adjustment for age, APACHE II score, presence of shock, site of infection, adequacy of antibiotics, species of infecting organism, and neutropenia. A preliminary report of a large, open-label trial in 250 patients indicated that HA-1A reduced the expected mortality by about 40 percent in the cohort of patients with gram-negative bacteremia and shock at the time of treatment.[2] This has now been confirmed in 750 patients. Thus, the results of the placebo-controlled clinical trial of HA-1A are consistent, reproducible, and not confounded. We disagree with the implication that patients who receive inadequate antibiotic treatment should be excluded from the analysis, because omitting them reduces the power of the study and the applicability of the results to clinical practice. It should be obvious that there was no effect of HA-1A treatment seen at centers with a low mortality, since the numbers of deaths and the total numbers of patients at these sites were so small that there was insufficient power to detect any possible treatment effect. We previously conducted the analyses referred to by Warren et al. and found that the use of risks in individual patients rather than raw APACHE II scores did not alter the P value for the effect of HA-1A. Warren et al. do not point out that there were some poor prognostic factors, such as cancer and polymicrobial bacteremia, that were more frequent in the HA-1A group. Finally, we have shown that adjustment for the time from diagnosis to treatment with HA-1A or placebo does not significantly decrease the efficacy of HA-1A (Table 1).

In conclusion, the published literature and the data presented at the meeting of the FDA advisory panel provide consistent and compelling evidence that HA-1A reduces mortality in patients with sepsis who have gram-negative bacteremia. On the basis of this evidence, the panel voted unanimously to recommend licensure. Most major European countries have already licensed HA-1A. The clinical trial of this antibody reported in the *Journal*[3] tested the hypothesis that HA-1A would reduce mortality in patients with sepsis who have gram-negative bacteremia. The null hypothesis was rejected, and no new hypotheses were generated. We believe that conducting additional placebo-controlled trials of HA-1A in the same population of patients is unwarranted and would be unethical. A recent independent analysis[4] has indicated that HA-1A will be cost effective if used in accordance with the enrollment criteria for the clinical trial just discussed.[3] The authors of this article estimated that appropriate use of HA-1A could save as many as 21,000 lives a year in the United States alone.[4]

Table 1. Effect of Time from Diagnosis to Treatment on the Efficacy of HA-1A in Patients with Gram-Negative Bacteremia.*

Hours from Diagnosis to Treatment	Study Group		Percent Reduction in Mortality with HA-1A
	Placebo (N = 95)	HA-1A (N = 105)	
	deaths†/no. of patients studied (%)		
0–6	20/37 (54)	10/32 (31)	43
>6–12	6/18 (33)	4/15 (27)	18
>12–18	2/7 (29)	3/15 (20)	31
>18	17/33 (52)	15/43 (35)	33

*Adjustment for time from diagnosis did not significantly decrease the efficacy of HA-1A (P = 0.022 by the Cochran–Mantel–Haenszel test).

†Figures represent mortality from all causes at 28 days after enrollment.

Elizabeth J. Ziegler, M.D.
San Diego, CA 92103 University of California Medical Center

Craig R. Smith M.D.
Malvern, PA 19355 Centocor, Inc.

1. Warren HS, Danner RL, Munford RS. Anti-endotoxin monoclonal antibodies. N Engl J Med 1992;326:1153-7.
2. Open Meeting of the Vaccines and Related Biological Products Advisory Committee, September 4, 1991. Vol. 1. Bethesda, Md.: Food and Drug Administration, 1991:39-44. (Obtained through the Freedom of Information Act.)
3. Ziegler EJ, Fisher CJ Jr, Sprung CL, et al. Treatment of gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin — a randomized, double-blind, placebo-controlled trial. N Engl J Med 1991;324:429-36.
4. Schulman KA, Glick HA, Rubin H, Eisenberg JM. Cost-effectiveness of HA-1A monoclonal antibody for gram-negative sepsis: economic assessment of a new therapeutic agent. JAMA 1991;266:3466-71.

BOOK REVIEWS

Textbook of Internal Medicine

Second edition. Edited by William N. Kelley, with 10 others. 2441 pp., illustrated. Philadelphia, J.B. Lippincott, 1992. $99.

To review this encyclopedic work required a strategy consistent with the way a textbook is usually used. I chose to read each chapter relating to the principal diagnoses of all patients admitted to my general medical service at a busy county hospital during a four-week period. My review is based on these chapters as well as those of particular personal interest.

In an era when pressures for cost containment, high expectations of patients, and defensive medical practices are constantly at loggerheads, the editors set the formidable goal of compiling a textbook of medicine that provides "realistic approaches to management" and maintains "currency, comprehensiveness, and clarity." With expertise and consistency, this emphasis on efficiency and effectiveness in medical practice resonates throughout the text. It is an

important accomplishment that separates this work from other major works in internal medicine.

Each of the 11 subspecialty areas is divided into three sections, dealing with the scientific basis of the discipline, specific disorders, and approaches to diagnosis and management. The separation of physiology, clinical and pathological descriptions, and management will be disconcerting to some readers. Depending on the clinical question, this organizational style can require the frequent use of the table of contents and index. Overall, however, it is a style that should make the book useful to readers at different levels of training. For example, the medical student can readily focus on physiology, while the practitioner can turn to options in diagnosis and treatment.

The writing throughout the text is remarkably consistent and clear. Without exception, I found the descriptions of disease, the recommendations of diagnostic strategies, and the treatment options carefully and specifically worded.

At first I was skeptical about how realistic it was for a multiauthored "encyclopedic textbook" to attempt to provide guidance about cost effectiveness. Perhaps Kelley et al. had found the Holy Grail, the answers to the brouhaha over outcomes research. I was pleasantly surprised to find excellent recommendations about the process of diagnosis and therapeutic strategies. Most important, the authors of virtually all the chapters that I reviewed presented a hierarchy of recommendations based on solid, albeit admittedly sometimes imperfect, scientific evidence. The reader is given the best approach or approaches according to the medical literature, often supplemented with recommendations that reflect the author's personal experience. These personal recommendations have the feeling of an expert consultation from a trusted colleague.

The chapters in the first section, "Principles of Medical Practice," are quite informative. They provide a context for the rest of the work. The authors repeatedly emphasize efficiency and flexibility in the practice of medicine and the dilemmas created by limitation of resources. The brief chapter on the history of medicine is succinct, provocative, and fun to read.

No textbook of medicine is going to satisfy all students of medicine. I quibbled openly with some therapeutic recommendations the way one does on rounds with residents or colleagues. Each of the recommendations, however, was well within the acceptable range of management options. There were a few typographic errors that surprised me, since I was not looking for them and I am certainly not a proofreader. Actually, I thought that computers fixed everything.

Many chapters end with a box that cross-references the material in the chapter to related topics elsewhere in the book. I did not find this a particularly helpful device, because the cross-references are very broad and occasionally somewhat obtuse.

The shelves are crowded with high-quality textbooks of medicine. Choosing a particular reference work reflects a personal preference for the style of the book. *Textbook of Internal Medicine* has everything that a student of medicine could ask for: clarity of style, consistency of purpose, and guidance in principle. I will return to this book time and again because it helps me to know and to practice medicine.

Max Michael, III, M.D.
Cooper Green Hospital
Birmingham, AL 35233

Clinical Epidemiology: A basic science for clinical medicine

Second edition. By David L. Sackett, R. Brian Haynes, Gordon H. Guyatt, and Peter Tugwell. 441 pp., illustrated. Boston, Little, Brown, 1991. $32.50.

The first edition of this book was published in 1985, and it quickly became a standard textbook for medical students and house officers. For many physicians, it was their introduction to the principles of test evaluation and critical reading of the medical literature. Although the first edition hardly seems dated, Sackett and his colleagues at McMaster University have added a new author (Guyatt) and issued a second edition. The new version retains the refreshing style and clear vision of the original, and new material has added vigor and relevance to the authors' teaching.

Unlike several of this book's competitors, *Clinical Epidemiology* has the feel of a work written for clinicians by clinicians who also happen to be scholars. Between editions, Sackett repeated his residency in internal medicine, and perhaps as a result, the many clinical vignettes used to illustrate points throughout the book will seem familiar yet fresh to the practicing physician. However, these authors are advancing an approach to medicine that does not rely on one's most recent experience, but instead integrates common sense with a scientific evaluation of available knowledge.

As before, the two main sections of the book address principles of diagnosis and management. A long chapter on "The Interpretation of Diagnostic Data" takes the reader from a basic discussion of how one chooses a threshold for designating a test result as abnormal, through Bayesian analysis, to decision analysis and utility theory. However, because the intellectual content has been integrated with recurring clinical cases, the chapter reads like the world's best attending rounds. Other fine chapters are aimed at helping physicians evaluate therapies on the basis of the medical literature and assess the effectiveness of therapies in their own patients.

The final section of the book outlines strategies for physicians to improve their own performance. The first edition contained a chapter on how to read a medical journal; the edition for the 1990s also describes how to perform computerized literature searches with the use of data bases such as MEDLINE and tools such as CD-ROM. Many of the book's principles are summarized on five laminated rulers that come in an envelope in the back of the book. Because they slip so easily from this pocket, their main purpose may be to induce a sense of loss in readers within the first few hours of possessing this book.

This is not a book for young investigators who are designing their first studies. For example, none of the chapters are intended to help a researcher choose the best study design for an investigation, nor does any address how one measures clinical states and health status, or provide an overview of statistics. Some readers will pick up this book expecting such material, but it succeeds in its intended mission. It is not a manual for an arcane science; *Clinical Epidemiology* is about practicing medicine to the best of one's abilities. This edition would be a fine addition to any medical school curriculum as well as any physician's bookshelf.

Thomas H. Lee, M.D.
Brigham and Women's Hospital
Boston, MA 02115

Diffuse Diseases of the Lung: A team approach

By W.M. Thurlbeck, Roberta R. Miller, Nestor L. Müller, and Edward C. Rosenow III. 243 pp., illustrated. Philadelphia, B.C. Decker, 1991. $82. (Distributed in the U.S. by Mosby-Year Book, St. Louis.)

Two pathologists, a radiologist, and a chest physician have collaborated to produce a book on a heterogeneous group of pulmonary diseases. According to the preface, what the diseases have in common is the fact that "they frequently come to biopsy for diagnostic purposes."

Introductory chapters briefly review the normal and abnormal structure and function of the lungs. Another chapter discusses diagnostic procedures, including imaging techniques, bronchoalveolar lavage, transbronchial biopsy, and open lung biopsy. The importance of the team approach to diagnosis is emphasized, in which the radiologist, internist, surgeon, and pathologist work in concert. For example, radiographic and CT findings can direct the surgeon to the most appropriate site for lung biopsy, and clinical and radiographic information can help in the interpretation of the biopsy findings.

The remaining 10 chapters of the book cover a multitude of diffuse pulmonary diseases, including acute and chronic infiltrative lung diseases, diffuse pulmonary hemorrhage, collagen vascular disease, pneumoconiosis, chronic airflow obstruction, and pulmonary